REMARKS

Claims 5-7 and 15-22 are pending in this application. Claims 3 and 4 have been allowed. Claims 1-2 and 8-14 have been canceled. Claims 5, 15, 16, 17, and 22 have been amended. Support for these amended claims can be found, for example, in the specification and claims as originally filed, on page 8 lines 31-34 and on page 9 lines 14-17. New claims 23-28 have been added. Support for new claim 24 can be found, for example, in the specification and claims as originally filed, on page 8 lines 31-34 and on page 9 lines 14-17. Support for new claims 23, 25, 26, and 28 can be found, for example, in the specification and claims as originally filed and on page 14 lines 20-28. Support for new claim 27 can be found, for example, in Example 5.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Allowed Claims

Applicant respectfully thanks the Examiner for allowing claims 3-4.

Rejections under 35 U.S.C. §103 (a)

Claims 5-7 and 15-22 stand rejected under 35 U.S.C. §103(a). The Examiner has maintained the previous rejection of claims 5-7 and 15-21 based on Brana et al., U.S. Patent No. 5,420,137 ("Brana I") in view of Brana et al., U.S. Patent No. 5,552,544 ("Brana II"). Applicant respectfully traverses the rejection.

The Examiner has presented a modified rejection based on Torres et al., Drug Development & Industrial Pharmacy, 21(2), 185-197 (1995) ("Torres"). It is unclear from the Office Action (i) whether Torres has been asserted alone or in combination with the '137 patent, and (ii) whether Torres has been asserted against claims 5-7 and/or claims 15-22. As such, Applicant has addressed each scenario below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicant asserts that the Examiner has failed to present a *prima facie* case of obviousness.

1. Claims 5, 15, 17, and 22 are not obvious over Brana I and Brana II.

As currently amended, claims 5, 15, 17, and 22 each require that "at least 1.5 mole equivalents" of two amine groups of a naphthalimide are protonated. Neither Brana I nor Brana II provide a suggestion or the motivation to modify their processes for preparing amonafide monohydrochloride to reach the present invention. The Examiner cited Brana I as teaching "a process of making the amonafide hydrochloride by adding hydrochloride dropwise and stirring vigorously . . . [and] it would be obvious that if one stirred it for a longer time it would yield the dihydrochloride salt." See page 3 of the Office Action mailed October 24, 2005. However, this does not suggest to a person of ordinary skill to modify the process in order to make a naphthalimide salt where "at least 1.5 mole equivalents" of the two amine groups are protonated as required by the claims.

Brana I discloses the preparation of amonafide monohydrochloride by adding 1 ml of 35% strength hydrochloric acid (0.01 moles of HCl) to 3 g of amonafide (0.01 moles of amonafide) dissolved in ethanol, shaking vigorously, cooling, and filtering to recover the monohydrochloride crystals. Col. 2 lines 57-64. Example E describes a process of preparing an injection concentrate as a lyophilisate. It is disclosed that water and NaOH are added to solid amonafide dihydrochloride (Amonafide.2HCl) to form a solution of monohydrochloride amonafide, which is sterilized and freeze-dried. The pH of the reconstituted solution is given as 5.5 ± 0.5. However, the titration curve on page 17 of the instant specification shows at pH 5-6 amonafide is primarily in the monohydrochloride form and less than one-half of the other amine group is protonated. Therefore, the claims are novel and non-obvious over Brana I. Brana II

discloses that its compounds "can be converted to their salts in a conventional manner, for example by reaction with an acid." Col. 2 lines 27-29.

Neither Brana I nor Brana II teach or suggest modifying these methods to (1) produce a salt "wherein at least 1.5 mole equivalents" of the two amine groups are protonated, as required by the claims. Thus, the Examiner has not established a *prima facie* case of obviousness. Applicant respectfully requests the withdrawal of this rejection.

2. Claim 5 is not obvious over Torres and Brana I or over Torres alone.

As Torres is directed to the design and formulation of tablets of amonafide, Applicant assumes that the Examiner did not intend this reference to apply to claims 5-7. As such, Applicant will address it below in relation to claims 15, 17, 22, and those claims depending therefrom.

3. Claims 15, 17, and 22 are not obvious over Brana I and Torres.

As currently amended, claims 15, 17, and 22 each require a salt "wherein at least 1.5 mole equivalents" of the two amine groups are protonated, and an "aqueous solution." The Examiner has not established a *prima facie* case of obviousness as to these claims. There is no suggestion or motivation provided by the references to reach the present invention. Torres does not provide a suggestion or motivation to modify its process of preparing amonafide tablets to make an "aqueous solution" as required in claims 15, 17 and 22. The Examiner asserts Torres discloses that amonafide 2HCl is "highly hygroscopic [and] . . . has bad flow properties and low compressibility," and then argues that this "would make it obvious and convenient to make its aqueous solution to make injectable solution." See page 2 of the Office Action.

The Applicants respectfully disagree. Torres' discussion of the problems associated with preparing amonafide 2HCl tablets does not provide the suggestion or motivation to make an amonafide solution. Rather, it denotes a problem working with the compound and a possible means to overcome it. For example, Torres discloses that the "hygroscopic behaviour of amonafide 2HCl (4) makes it necessary to work under controlled relative humidity environments

lower that 48%." See page 186 last paragraph. As to the bad flow properties and low compressibility of amonafide 2 HCl, Torres discloses through "a wet granulation process, the characteristics of the material for compression improve significantly." See page 196 under CONCLUSIONS. In addition, the reference notes that "[t]wo formulations of tablets of amonafide obtained by wet granulation . . . meet all the requirements for this pharmaceutical form and therefore are valid for the oral administration of the antineoplastic drug. *Id.* Torres presents wet granulation as a way to overcome the problems associated with making amonafide tablets. However, an amonafide 2HCl "aqueous solution" is not part of Torres' solution to the problems associated with preparing amonafide tablets.

Brana I cannot cure the defects of Torres because it provides no suggestion or motivation to modify the teachings of Torres to make the present invention. As discussed above, Brana I does not teach or suggest to a person of ordinary skill in the art a salt "wherein at least 1.5 mole equivalents" of the two amine groups are protonated. Moreover, even if modified Torres provides no reasonable expectation of success to practice the present invention. As discussed above, Torres discloses the preparation of amonafide 2HCl tablets. There is no reasonable expectation of success that the a modified Torres process of making amonafide 2HCl tablets would yield an "aqueous solution" as required by claims 15, 17, 22, and those claims depending therefrom. Thus, the Examiner has not established a *prima facie* case of obviousness. Applicant respectfully requests the withdrawal of this rejection.

4. Claims 15, 17, and 22 are not obvious over Torres alone.

As previously discussed, Torres' disclosure is limited to the design and formulation of tablets. As such, it does not disclose an "aqueous solution" as required by claims 15, 17, 22, and those claims depending therefrom. Therefore, it alone cannot form the basis of an obviousness rejection.

The Examiner has not established a *prima facie* case of obviousness. For the reasons set forth above, Applicant asserts that claims 5-7 and 15-22 are non-obvious over the cited references and requests withdrawal of the rejection.

CONCLUSION

The present application is therefore in condition for allowance. Early and favorable notification thereof is respectfully requested. If the Examiner believes there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,
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Dated: March 24, 2006 By: J. P. Bernhardt

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